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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,472	12/19/2005	Signe M. Christensen	22460-003US1 / 1015US2	4416

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/23/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/535,472	CHRISTENSEN ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-47,54-60,62 and 65-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-47,54-60,62 and 65-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/30/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/3/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 10/30/2008, claims 43-47, 54-60, 62, and 65-70 are pending and examined herein.

Election/Restrictions---reiterated

The previous Action acknowledged Applicant's elections as follows:

With regard to claim 43, applicant elects "A-B-C" and "2'-deoxy-erythro-pentofuranosyl."

With regard to claim 46, applicant elects "oxy-LNA" and "beta configuration."

With regard to claims 54-62, applicant elects, 4, 5, 5, 16, and 7, respectively.

With regard to claim 64, applicant elects "O-P(O)2-O-."

With regard to claim 68, applicant elects "chemotherapeutic compounds."

Specification/Sequence Compliance

The previous Action objected to the disclosure because several sequences were set forth in the specification without accompanying SEQ ID NO: identifiers. See also Notice to Comply mailed therewith. Thus, the specification as filed does not comply with the requirements above,

in particular 1.821(d) at least, because it contains nucleotide sequences of over 10 nucleobases each that are not identified by accompanying sequence identifiers. For example, several sequences are set forth at pages 27-29 and 32-42 without corresponding SEQ ID NO: identifiers. This is but a sampling of the many sequences set forth in the instant application without SEQ ID NO: identifiers. Applicants were advised to review the entire application—claims, drawings, and specification—for complete compliance with the Sequence Rules. Thus, the Examiner notes herein that the above listing of pages and figures which set forth examples in the specification of nucleotide sequences that require SEQ ID NO: is by way of illustration. In order to be fully responsive to this Office Action, Applicant should review this application in its entirety to ensure compliance with the requirements of 37 CFR 1.821 through 1.825 and to make all appropriate corrections.

However, in the reply filed 10/30/2008 Applicant has not responded to or supplied the missing SEQ ID NO identifiers or provided a sequence listing containing said identifiers. Accordingly, the objection is maintained. The application remains out of sequence compliance, and no sequence listing is found in the instant application.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 43-47, 54-60, 62, and 65-68 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43, 47-51, 53, 55-96 of copending Application No. 10/717,434.

Although the conflicting claims are not identical, they are not patentably distinct from each other because conflicting application 10/717434 claims an oligonucleotide having the formula A-B-C-D, wherein A represents a sequence of locked nucleotide units; B represents a sequence of non-locked nucleotide units, wherein B has a length of 4-20 nucleotide units; C represents a sequence of locked nucleotide units; and D represents a non-locked nucleotide unit or a sequence of non-locked nucleotide units. In certain embodiments the LNAs of A and C may be beta-D-oxy-LNA units; the oligo may contain phosphorothioate linkages; and B represents a sequence able to recruit RNase H.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant does not traverse the rejection.

Claim Rejections - 35 USC § 112 (Enablement)---withdrawn

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 43-47, 54-60, 62, and 65-68 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of Applicant's amendments to the claims. The rejection is not applied against new claim 70 in view of Applicant's arguments, which are considered persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43-47, 54-60, 62, and 65-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurreck et al. (2002) *Nucleic Acids Res.* 30:1911-1918 in view of:

1. Keinicke et al. (2002) "Alpha-L-RNA (alpha-L-ribo configured RNA): synthesis and RNA-selective hybridization of alpha-L-RNA/alpha-L-LNA chimera" *Bioorganic & Medicinal Chemistry Lett.* 12:593-596;
2. Sorensen et al. (2002) "Alpha-L-ribo-configured locked nucleic acid (alpha-L-LNA): synthesis and properties" *J. Am. Chem. Soc.* 124:2164-2176;

3. Orum et al. (WO 01/48190 A2) "Therapeutic uses of LNA-modified oligonucleotides";
4. Wahlestedt et al. (2000) "Potent and nontoxic antisense oligonucleotides containing locked nucleic acids" *Proc. Natl. Acad. Sci.* 97:5633-5638; and
5. Monia et al. (US Patent 6,884,787).

The instant claims read on LNA-DNA-LNA gapmers, mixmers, and chimeras comprising one or more alpha-L-oxy LNA nucleotides. The claims embrace compounds and compositions for in vitro or in vivo uses.

Kurreck et al. taught LNA/DNA mixmers, gapmers, and end blocks, 18-nucleotides in length, capable of inducing RNase H–mediated cleavage of a complementary mRNA target (Table 1, page 1912; and pp. 1913-4). More specifically, Kurreck et al. taught 18-nucleotide LNA-DNA-LNA mixmers, gapmers, and end blocks, having first and second regions (A and C) of at least 1 to 5 oxy LNA monomers in the beta configuration flanking a third, or central, region (B) consisting of DNA and optionally 1 or 2 LNAs (see Table 1). The central DNA gap, which in certain embodiments has at least one LNA, is said to be necessary for recruitment of RNase H (page 1913-4 and 1916-7). In fact, with the exception of LNA 21, each of the oligos disclosed in Table 1 therein has RNase H-mediated mRNA cleavage activity.

Kurreck et al. do not teach alpha-L-oxy LNA nucleotides, or oligonucleotides containing this particular configuration. Further, Kurreck et al. do not teach LNA/DNA oligonucleotides containing phosphorothioate linkages, or compositions comprising oligos and chemotherapeutic

compounds. Kurreck et al. further do not teach LNA-DNA-LNA gapmers 16 nucleotides in length.

However, the prior art is replete with disclosures teaching methods and materials for making and using RNase H active, alpha-L-oxy LNA-containing, phosphorothioate oligonucleotides.

For example, Keinicke et al. taught the synthesis and incorporation of α-L-LNA (α-L-ribo configuration) nucleotides into short oligonucleotides (pp. 593-596). Testing several LNA/RNA and LNA/DNA mixmers (Table 2), Keinicke et al. showed and taught that the incorporation of three α-L LNA monomers into a DNA oligonucleotide significantly improves the thermal stability towards both DNA and RNA as compared to standard DNA oligos. It is further shown that α-L-LNA-containing oligonucleotides display improved hybridization properties to RNAs as well as satisfactory discriminatory behavior (page 595). In addition, Keinicke et al. taught that α-L-LNAs confer enhanced stability to nuclease digestion as compared to an all DNA oligonucleotide (page 595). In concluding, Keinicke et al. state that their results suggest further studies to evaluate the full potential of the α-L-LNA oligos as antisense oligonucleotides, suggesting that in general the α-L-LNA oligos might be expected to have reduced toxicity and improved specificity as compared to current antisense molecules.

Sorensen et al. taught and showed that α-L-LNA/DNA mixmers are capable of recognizing complementary RNA targets with high specificity, and are resistant to nuclease degradation. Sorensen et al. further show that α-L-LNA-containing oligonucleotides are capable of triggering RNase H mediated degradation of a complemenary RNA target, and further suggest

using such oligos in a steric blocking capacity, thereby recommending their use as antisense oligonucleotides (pp. 2169-2171).

Orum et al. taught methods for making and using phosphorothioated, α-L-oxy-LNA-containing antisense oligonucleotides and pharmaceutical compositions thereof for inhibiting the expression of a gene in a cell in vitro and in vivo. It is said the LNA oligonucleotides may be used in combination with chemotherapeutic drugs (pp. 9-11, 17, 28-29, see also 1-43).

Wahlstedt et al., cited by Applicant in the Remarks filed 10/30/2008, traversing the enablement rejection, is said to show that one of skill would reasonably expect many different types of antisense oligonucleotides to be capable of inhibiting the expression of a gene. Applicant states Wahlstedt et al. conducted studies using a 15 residue oligonucleotide targeted to the rat 6-opiod receptor. The oligonucleotide consisted of 4 LNA residues followed by 6 DNA residues and then 5 LNA residues (DOR-AS-1 LNA/DNA/LNA gap-mer). The oligonucleotide was injected into the cerebrospinal fluid of rats. The treatment knocked down expression of DORY a G-protein coupled receptor and altered the response of the mice to pain in the presence of an opiate. Thus, the DOR-AS-1 **LNA/DNA/LNA** gap-mer had a marked en vivo effect. Thus, oligonucleotides can reach targets en vivo and **exert** a physiological effect. Wahlestedt et al. conclude that the tested oligonucleotides containing DNA and LNA cxhibitcd "(i) biological stability, (ii) RNase H activation, (iii) lack of toxicity, and (iv) potent biological activities." Applicant states, while Wahlstedt et al. do not exemplify α-L-oxy-LNA-containing oligonucleotides, this is no reason to doubt the oligos of the instant claims would no be likewise be effective in vivo.

Furthermore, the prior art is replete with disclosures teaching and recommending the use of antisense chimeras or gapmers of various lengths, comprising a central DNA gap flanked by one or more modified or non-standard nucleotides and one or more phosphorothiates to protect the antisense oligonucleotide against nuclease degradation while preserving RNaseH activity. It is clear from the prior art that it was well known at the time of invention that LNAs, 2'-sugar modifications, and phosphorothioates could be used alone and in combination to optimize the stability, solubility, cellular uptake, and activity of antisense oligonucleotide.

Thus, with regard to claims 65-67, in addition to the disclosure of Kurreck et al. teaching the benefits and utilities of LNA-DNA-LNA gapmers, Monia et al. taught that antisense oligonucleotides may be synthesized as composite structures of two or more modified oligonucleotides and/or oligonucleotide mimetics wherein the arrangement of said nucleotides is in the form referred to in the art as "gapmers" (col. 12). It is taught that preferred modifications include phosphorothioate linkages, locked nucleic acids, and 2'-sugar modifications (cols. 8-9). It is taught that these modifications may be combined and incorporated into the same antisense compound to optimize its activity (col. 12, lines 23-35). With regard to claims 59 and 60, Monia et al. taught that antisense compounds can be anywhere from 8 to 50 nucleotides in length, preferably 12-30 nucleotides in length. Thus, for example, an oligo may be 12, 13, 14, 15, or 16 nucleotides in length

Methods and materials for making LNA-containing oligonucleotides were well known in the prior art, as evidenced by Kurreck et al., Monia et al. (col. 9, citing prior art, and col. 12, bottom bridging to 13), Keinicke et al., Sorensen et al., and Orum et al.

Thus, with regard to claims 59 and 60, absent evidence of secondary considerations, the particular length of the antisense oligonucleotide does not patentably distinguish the claimed invention from the prior art, since one of skill would reasonably anticipate LNA-DNA-LNA gapmers and chimeras of lengths in the range disclosed by the prior art to have the same general properties, varying in degree only and not in kind.

With regard to claim 70, both Orum et al. (page 28) and Monia et al. taught that antisense olignucleotides, including chimeras and gapmers, may be formulated in pharmaceutical compositions with one or more chemotherapeutic agents (col. 28, lines 1-10).

Accordingly, the prior art is replete with disclosure teaching and recommending the use of LNA/DNA gapmers and chimeras of the type now claimed, as well as countless other varieties in antisense oligonucleotides of various lengths from about 8 to 50 bases. The benefits and utilities of such LNA-containing compounds is clearly set forth in the prior art, as represented by the references cited herein. Methods and materials for making and using a variety of LNA-DNA-LNA gapmers were widely available, and the level of skill in the art for making and testing such constructs was high. Several exemplary embodiments were available in the prior art, teaching and recommending the use of LNA/DNA gapmers and mixmers of both the α and β configurations. The combination of prior art as a whole cited herein clearly show that multiple sugar-phosphate backbone modifications may be incorporated into the end-flanking regions as well as the central region of an oligo to improve its properties. Thus, one of skill would have had a reasonable expectation of success and ample reason to make and use LNA/DNA compositions of the type now claimed.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Applicants' Arguments

Applicants' arguments presented on 10/30/08 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
December 17, 2008